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Association of Cardiovascular Risk Factors With MRI Indices of Cerebrovascular Structure and Function and White Matter Hyperintensities in Young Adults

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IMPORTANCE Risk of stroke and brain atrophy in later life relate to levels of cardiovascular risk in early adulthood. However, it is unknown whether cerebrovascular changes are present in young adults.

OBJECTIVE To examine relationships between modifiable cardiovascular risk factors and cerebrovascular structure, function, and white matter integrity in young adults.

DESIGN, SETTING, AND PARTICIPANTS A cross-sectional observational study of 125 young adults (aged 18-40 years) without clinical evidence of cerebrovascular disease. Data collection was completed between August 2014 and May 2016 at the University of Oxford, United Kingdom. Final data collection was completed on May 31, 2016.

EXPOSURES The number of modifiable cardiovascular risk factors at recommended levels, based on the following criteria: body mass index (BMI) <25; highest tertile of cardiovascular fitness and/or physical activity; alcohol consumption <8 drinks/week; nonsmoker for >6 months; blood pressure on awake ambulatory monitoring <130/80 mm Hg; a nonhypertensive diastolic response to exercise (peak diastolic blood pressure <90 mm Hg); total cholesterol <200 mg/dL; and fasting glucose <100mg/dL. Each risk factor at the recommended level was assigned a value of 1, and participants were categorized from 0-8, according to the number of risk factors at recommended levels, with higher numbers indicating healthier risk categories.

MAIN OUTCOMES AND MEASURES Cerebral vessel density, caliber and tortuosity, brain white matter hyperintensity lesion count. In a subgroup (n = 52), brain blood arrival time and cerebral blood flow assessed by brain magnetic resonance imaging (MRI).

RESULTS A total of 125 participants, mean (SD) age 25 (5) years, 49% women, with a mean (SD) score of 6.0 (1.4) modifiable cardiovascular risk factors at recommended levels, completed the cardiovascular risk assessment and brain MRI protocol. Cardiovascular risk factors were correlated with cerebrovascular morphology and white matter hyperintensity count in multivariable models. For each additional modifiable risk factor categorized as healthy, vessel density was greater by 0.3 vessels/cm^3 (95% CI, 0.1-0.5; P = .003), vessel caliber was greater by 8 µm (95% CI, 3-13; P = .01), and white matter hyperintensity lesions were fewer by 1.6 lesions (95% CI, −3.0 to −0.5; P = .006). Among the 52 participants with available data, cerebral blood flow varied with vessel density and was 2.5 mL/100 g/min higher for each healthier category of a modifiable risk factor (95% CI, 0.16-4.89; P = .03).

CONCLUSIONS AND RELEVANCE In this preliminary study involving young adults without clinical evidence of cerebrovascular disease, a greater number of modifiable cardiovascular risk factors at recommended levels was associated with higher cerebral vessel density and caliber, higher cerebral blood flow, and fewer white matter hyperintensities. Further research is needed to verify these findings and determine their clinical importance.

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A life-course approach to understand the risk of cardiovascular disease is well established,[1] and it is accepted that changes in cardiac and vascular structure that underlie this risk emerge very early in life.[2,3] Whether modifiable cardiovascular risk factors and novel early life exposures, such as preterm birth, influence the early life cerebrovasculature is less well studied.

Cardiovascular risk closely relates to cerebrovascular injury and cognitive decline in older adults.[4] Magnetic resonance imaging (MRI) markers of cerebral injury in mid-life, including white matter hyperintensity lesions, are associated with future stroke, dementia, and all-cause mortality.[5] Progression of white matter hyperintensity lesions is faster in association with metabolic dysfunction and hypertension.[6] Experimental studies have demonstrated that cardiovascular risk factors result in remodeling of the brain vasculature, including vessel rarefaction, lower vessel caliber, and cerebral blood flow.[7] Elevated blood pressure, dyslipidemia, and low fitness in early adulthood are known to predict brain health in older adult life.[8-10] Whether cerebrovascular morphological changes are already evident in young adults and correlate with white matter hyperintensity lesions and risk factors at this age is unclear.

Advances in brain MRI allow automated segmentation and analysis of vessel morphology, white matter hyperintensity lesions,[11,12] and blood flow,[13] thus making it possible to estimate brain vascular and structural status for an individual.[11,12] Therefore, the objective of the current study was to use multimodality brain imaging to test the hypothesis that cardiovascular risk profiles are correlated with variation in vessel morphology and white matter hyperintensity lesions in young adults.

Key Points

Question Are modifiable cardiovascular risk factors in young adults associated with cerebral blood vessel structure and function and neuroimaging white matter hyperintensities?

Results In this cross-sectional study of 125 young adults without clinical evidence of cerebrovascular disease, a higher number of optimal cardiovascular health metrics was correlated with higher cerebral vessel density, higher cerebral blood flow, and lower number of white matter hyperintensity lesions.

Meaning These preliminary findings suggest a relationship between modifiable cardiovascular risk factors and biomarkers of cerebrovascular structure and function and white matter hyperintensities in young adults. Further research is needed to verify these findings and determine clinical importance.

Methods

Study Design and Participants

This was a cross-sectional observational study completed between August 2014 and May 2016. The South Central Research Ethics Committee for the National Health Service Health Research Authority (NHS HRA) approved the study. All participants gave written informed consent. Measurements were completed at the Oxford Cardiovascular Clinical Research Facility and Oxford Centre of Clinical Magnetic Resonance Research, John Radcliffe Hospital, University of Oxford, United Kingdom. Image analysis was performed using pipelines developed at the Hotchkiss Brain Institute, University of Calgary and Wellcome Centre for Integrative Neuroimaging, University of Oxford.[12-16] Final data collection was completed on May 31, 2016.

Participants aged 18 through 40 years were recruited via active and passive recruitment[17] including local advertising, invitation from local birth cohort studies, and invitation from the Oxford University Hospital Hypertension Service. Strategies were designed to recruit adults with a heterogeneity in risk factors known to be present in young adult populations including traditional risk factors, such as hypertension, and more novel factors such as gestational age at the time of a person's birth. Participants were excluded if they had previous cardiovascular or cerebrovascular events, renal dysfunction, or metabolic disease including diagnosis of familial hyperlipidemia. Participants with secondary causes of hypertension such as renal vascular disease, vascular anomalies, or adrenal dysfunction were excluded following assessment at the Oxford University Hospital Hypertension Service.

Cardiovascular Risk Assessment

Participants attended a research clinic in the morning after a 12-hour fast to complete a detailed cardiovascular risk assessment (Supplementary Data eMethods 1 in the Supplement). Measurements included body size; fasting blood samples for total cholesterol, high-density lipoprotein, low-density lipoprotein, triglycerides, highly sensitive C-reactive protein, glucose, and insulin levels; clinic and 24-hour blood pressure; and peak oxygen uptake and exercise blood pressure (from cardiopulmonary exercise testing). In addition, participants completed a detailed lifestyle questionnaire and had 7 complete days of objectively measured physical activity. Post hoc, participants were assessed for a cardiovascular score based on 8 modifiable risk factors, with 1 point awarded for each healthier category of a modifiable risk factor according to the following criteria: body mass index (BMI) less than 25; highest tertile of cardiovascular fitness and/or physical activity; alcohol consumption of less than 8 drinks/week; nonsmoker for more than 6 months; blood pressure on awake ambulatory monitoring lower than 130/80 mm Hg; a nonhypertensive diastolic response to exercise (peak diastolic blood pressure <90 mm Hg), total cholesterol level lower than 200 mg/dL; and fasting glucose level lower than 100 mg/dL. The score was adapted from established cardiovascular health scores to include alcohol consumption and dynamic exercise blood pressure response, as known independent risk factors for brain health.[18-20] The thresholds for healthy criteria were set to be consistent with recommended public health guidelines and existing literature.[4,9,18,19,21]

Brain Imaging and Analysis

Individuals underwent a multimodality MRI scan (3.0 T Trio Tim, Siemens). The MRI protocol included T1-weighted structural, T2-weighted fluid-attenuated inversion recovery (FLAIR),

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diffusion tensor imaging (DTI), and time-of-flight (TOF) MR arteriogram (MRA) (Supplementary Data eMethods 2 in the Supplement). MR imaging was completed in the fasting state and prior to exercise testing. Complete acquisition and analysis methods are presented in the Supplement.

T1-weighted images were processed using FMRIB Software Library (FSL) tools.[20] Brain vessel segmentation was completed on TOF MRA using previously described automated segmentation tools (eFigure 1 in the Supplement).[12,16] Binary segmentations were used to determine vessel density, caliber, and tortuosity.

White matter hyperintensity (WMH) lesions and associated volumes were segmented using the brain intensity abnormality classification algorithm (BIANCA); a fully automated, supervised method for WMH detection.[11,22] BIANCA classifies image voxels based on their intensity and spatial features, where the intensity features were extracted from T2-weighted FLAIR, T1-weighted and DTI fractional anisotropy images; these images were generated using DTI tools, FSL topup, FSL eddy, and DTIFit.[20,23] WMH masks were manually segmented from 10 images to use as the training set for BIANCA; these were independently verified by a neurologist (T.S.) and radiologist (D.M.) blinded to participant risk profile. Lesion count was selected as the most sensitive outcome of white matter change in young adults in whom a single lesion, independent of volume, could be considered abnormal.[24] Minimum lesion size used in our analysis was 1 mm^3.

A subgroup of 52 participants also had multidelay vessel-encoded pseudocontinuous arterial spin labeling (ASL), described in a previous protocol.[13] Cerebral blood flow and blood arrival time were estimated from ASL images using a previously described analysis pipeline.[13,15] Gray matter masks were used to calculate the average cerebral blood flow after linear registration of the ASL MRI to the T1-weighted MRI data set.

Statistical Analysis

Recruitment was continued to 125 participants for an estimated power of 90% at $P = .05$ to identify a 0.70-SD difference in vessel density, vessel caliber, and white matter lesion count between lowest and highest cardiovascular risk tertile groups. ASL MRI was added during the course of the study to provide a subgroup of 52 participants, recruited sequentially for an estimated 80% power to detect a 10% difference in cerebral blood flow.[25]

Existing literature on risk predictors of brain health was used to define an a priori set of potential correlates of MRI brain health in young adults.[4,9,18,19,21] These were grouped as (1) nonmodifiable, including age, sex, gestational age at birth, and (2) modifiable, including systolic blood pressure, BMI, peak exercise capacity (oxygen uptake), peak exercise diastolic blood pressure, weekly vigorous activity level, alcohol consumption, smoking history, lipid profile, glucose and insulin resistance, and current hypertension medication.

In a priori analysis, bivariable and multivariable analysis was completed to investigate correlation between the defined cardiovascular risk markers and brain imaging findings. In this multivariable analysis to reduce multiple testing and potential interaction between the variables, the model was restricted to a subset of variables (resting systolic blood pressure, BMI, vigorous physical activity level, alcohol consumption, and smoking). This model was adjusted for nonmodifiable factors including age, sex, and gestational age.

In post-hoc analysis, the individuals' combined cardiovascular score from across 8 risk factors was used as a metric of overall modifiable cardiovascular health. The relationships between the individuals' modifiable cardiovascular score and brain imaging findings were studied using linear regression adjusted for age and sex. Comparison between brain imaging findings was made between groups of participants in the lowest and highest tertiles for the cardiovascular score. The decision to use tertiles is based on evidence from longitudinal studies that observed that young adults in the lowest tertiles of cardiovascular fitness have an increased risk of stroke.[9]

In addition, bivariable analysis was completed to investigate correlation between vessel morphology and white matter hyperintensity lesion count and in a subgroup (n = 52), blood arrival time and cerebral blood flow. These relationships were further investigated with fixed entry linear regression models adjusted for modifiable and nonmodifiable factors used in the models above.

Statistical analysis was undertaken using SPSS version 22. Normality of variables was assessed by visual assessment of curves. If normally distributed, results are presented as mean (SD) for continuous variables, otherwise median (interquartile range [IQR]). For categorical variables, number and percentage are presented. Comparison between groups for continuous variables was performed with a 2-sided, independent-sample *t* test. All multivariable analysis was completed using forced entry linear regression with residual analysis completed to assess model assumptions. All multivariable analyses were adjusted for age and sex. All tests were 2-sided; $P < .05$ considered statistically significant with no adjustment for multiple comparisons. Due to multiplicity of testing all results were considered exploratory. Results are presented as point estimates and 95% CIs in units appropriate to the risk factor and brain imaging findings reported. Graphpad Prism 7 software was used for statistical figures, with mean (95% CI) presented.

Results

A total of 125 participants completed the brain MRI protocol and cardiovascular risk assessment study measures. Participants' mean (SD) age was 24.7 (5.0) years, 61 participants were women (49%), the mean (SD) gestational age at the time of their birth was 36.6 (4.3) weeks, 86 completed university-level education (68.8%), and 29 had a history of hypertension (of whom 21 were taking antihypertension medications) (16.8%) (**Table 1**). The mean (SD) score of modifiable cardiovascular risk factors at recommended levels was 6.0 (1.4). The distributions of MRI brain outcomes between lowest and highest quintile of the respective measures are presented in eTable 1 in the Supplement. The 52 participants with available cerebral blood flow data had a comparable demographic

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Table 1. Baseline Characteristics and Cardiovascular Risk Profiles

	Study Group (n = 125)
Demographics	
Age, mean (SD), y	24.7 (5.0)
Female, No. (%)	61 (49)
Gestational age, mean (SD), wk	36.6 (4.3)
Smoking, No. (%)	19 (15.2)
Median pack-years (IQR)	2.7 (6.7)
Alcohol consumption, No. (%)	97 (77.6)
Median drinks per week (IQR)	4.0 (4.0)
Hypertension diagnosis, No. (%)	29 (23.0)
Taking hypertension medication, No. (%)	21 (16.8)
Family history of stroke or CHD, No. (%)	10 (8)
Completed university-level education, No. (%)	86 (68.8)
Anthropometrics, mean (SD)	
Height, m	1.73 (0.1)
Weight, kg	70.9 (13.8)
Body mass index	23.6 (3.7)
Blood pressure, mean (SD), mm Hg	
Resting systolic	122.0 (11.6)
Resting diastolic	71.3 (9.55)
Ambulatory awake systolic	129.6 (11.8)
Ambulatory awake diastolic	76.9 (8.0)
Peak exercise systolic	174.8 (25.4)
Peak exercise diastolic	87.1 (12.4)
Fitness	
Peak $\dot{V}o_2$, mean (SD), mL/kg/min	37.9 (9.6)
Peak respiratory exchange ratio, mean (SD)	1.2 (0.06)
Vigorous physical activity, median (IQR), h/wk	0.74 (1.25)
Moderate to vigorous physical activity, median (IQR), h/wk	14.73 (6.09)
Biochemistry	
Total cholesterol, mean (SD), mg/dL	170.15 (29.0)
LDL, mean (SD), mg/dL	97.45 (25.9)
HDL, mean (SD), mg/dL	55.68 (11.2)
Total cholesterol:HDL ratio, mean (SD)	3.18 (0.85)
Triglycerides, median (IQR), mg/dL	74.4 (54.0)
Blood glucose, mean (SD), mg/dL	88.2 (7)
HOMA-IR, mean (SD)	0.77 (0.46)
hsCRP, median (IQR), mg/L	0.57 (1.16)
Brain MRI parameters, mean (SD)	
Brain vessel density, vessels/cm^3	8.3 (1.41)
Brain vessel caliber, µm	531 (36)
Brain vessel tortuosity[a]	1.49 (0.088)
Brain white matter hyperintensity lesion count	20.9 (7.9)
Brain blood arrival time, s (n=52)	1.01 (0.08)
Cerebral blood flow, mL/100 g/min (n=52)	60 (11.5)

Abbreviations: CHD, coronary heart disease; HDL, high-density lipoprotein; HOMA-IR, homeostatic model assessment of insulin resistance; hsCRP, highly sensitive C-reactive protein; IQR, interquartile range; LDL, low-density lipoprotein; MRI, magnetic resonance imaging.

SI conversion factors: To convert lipid values to mmol/L, multiply by 0.0259; triglycerides to mmol/L, multiply by 0.0113; glucose to mmol/L, multiply by 0.0555; and C-reactive protein to nmol/L, multiply by 9.524.

[a] Vessel tortuosity was defined by the deviation from the shortest path between 2 points. This analysis was implemented by identifying the vessel end points and bifurcations, calculating the shortest path and the length of the actual center line between each 2 connected points. The final tortuosity was then calculated by the ratio and it was averaged over all vessel segments.

profile as the overall study group (mean [SD] age, 24.6 [5.0] years, 42% women, gestational age 37.2 [3.6] weeks, and 10 taking antihypertension medications).

Modifiable Risk Factors, Brain Vessel Structure, and WMH Lesions

Association between risk factors (systolic blood pressure, BMI, smoking, exercise peak diastolic blood pressure, cholesterol/HDL ratio, hypertension treatment) and brain vessel morphology is presented in **Table 2**. Vessel tortuosity only varied with gestational age in both bivariable and adjusted models (0.005-unit tortuosity change/gestational week [95% CI, 0.001-0.009], P = .007) (Table 2; and eTable 2 in the Supplement).

In the multivariable models, systolic blood pressure (-0.02 vessels/cm^3 per mm Hg [95% CI, −0.04 to −0.0004], P=.046), smoking (0.17 vessels/cm^3 per pack-year [95% CI, 0.06 to 0.28], P=.004), and BMI (−0.08 vessels/cm^3 per 1 BMI unit [95% CI, −0.15 to −0.01], P = .02) were significantly correlated with vessel density. Vessel caliber was correlated with systolic blood pressure (−0.6 µm per mm Hg [95% CI, −1.0 to −0.05], P = .03) and smoking (4.0 µm per pack-year [95% CI, 0.2 to 8.0], P = .04).

In bivariable models, the number of WMH lesions correlated with smoking (0.8 lesions per pack-year [95% CI, 0.15-1.44], P = .02), exercise diastolic blood pressure (0.1 lesion per mm Hg [95% CI, 0.01-0.24], P = .04), and alcohol consumption (0.4 lesions per weekly alcoholic drink [95% CI, 0.03-0.8], P = .03) (eTable 3 in the Supplement).

Healthier categories on the modifiable cardiovascular score correlated with vessel morphology (**Table 3**). Each additional healthier category of risk factor was associated with a 0.3-vessels/cm^3 higher vessel density (95% CI, 0.1-0.5, P = .003) and 8-µm greater vessel caliber (95% CI, 3.0-13.0, P = .01).

Similarly, WMH lesion count correlated with the cardiovascular score, with 1.6 fewer WMH lesions per additional healthier category of risk factor (95% CI, −3.0 to −0.5, P = .006). In addition, the cardiovascular score correlated with total volume of WMH adjusted for brain size, with 51-mm^3 lower WMH lesion volume per additional healthier category of risk factor (95% CI, to −87 to −15 mm^3, P = .006). The **Figure** displays differences in vessel morphology and WMH lesions among tertiles of the group, divided based on the cardiovascular score.

Vessel Morphology and Cerebral Blood Flow, Arrival Time, and White Matter Lesion Count

To explore whether cerebral blood flow also varied with cardiovascular risk factors, a subgroup (n = 52) analysis was performed in those with cerebral blood flow measures (mean cerebral blood flow, 60 mL/100 g/min [SD, 11.5] and mean blood arrival time, 1.01 seconds [SD, 0.08]). Slower blood arrival time (0.1 seconds per 1 kg/m^2 [95% CI, 0.001 to 0.05], P = .001) and lower cerebral blood flow (−1.1 mL/100 g/min per 1 kg/m^2 [95% CI, −2.0 to −0.1], P = .03) were correlated with higher BMI (eTable 3 in the Supplement). Cerebral blood flow was also lower in correlation with antihypertensive medication (11 mL/100 g/min [95% CI, −18 to −3], P = .007). Cerebral blood flow was 2.5 mL/100 g/min higher for each additional healthier category of the cardiovascular score (95% CI, 0.16 to 4.89,

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Table 2. Association Between Nonmodifiable and Modifiable Risk Factors and Brain Vessel Morphology (Vessel Density, Caliber, and Tortuosity)[a]

	Bivariable Point Estimate (95% CI)	*P* Value	Multivariable-Adjusted Point Estimate (95% CI)	*P* Value
Brain Vessel Density, vessels/cm^3			R^2 = 0.20	**.009**
Gestational age, per week	−0.001 (−0.06 to 0.06)	.98	−0.02 (−0.08 to 0.03)	.42
Resting SBP, per mm Hg	−0.03 (−0.05 to −0.004)	.02	−0.02 (−0.04 to −0.0004)	.046
BMI, per unit	−0.10 (−0.16 to −0.02)	.01	−0.08 (−0.15 to −0.01)	.02
Vigorous physical activity, per hours per week	0.10 (−0.17 to 0.39)	.42	−0.04 (−0.28 to 0.20)	.75
Alcohol intake, per drinks per week	−0.10 (−0.025 to −0.008)	.31	−0.01 (−0.04 to 0.02)	.41
Smoking, per pack-year	0.20 (0.06 to 0.30)	.004	0.17 (0.06 to 0.28)	.004
Peak $\dot{V}o_2$, per mL/kg/min	0.01 (−0.02 to 0.04)	.5		
Peak exercise diastolic blood pressure, per mm Hg	−0.02 (−0.04 to −0.003)	.047		
Cholesterol/HDL ratio, per unit	−0.40 (−0.69 to −0.06)	.02		
HOMA-IR, per unit increase	−0.56 (−1.17 to 0.04)	.07		
Hypertension treatment (vs no treatment)	0.75 (−0.01 to 1.5)	.05		
Brain Vessel Caliber, µm			R^2 = 0.24	.001
Gestational age, per week	−0.1 (−2.0 to 1.0)	.88	−1.0 (−3.0 to 0.5)	.16
Resting SBP, per mm Hg	−0.4 (−1.0 to 2.0)	.15	−0.6 (−1.0 to −0.05)	.03
BMI, per unit	−1.0 (−3.0 to 1.0)	.33	−1.0 (−3.0 to 1.0)	.42
Vigorous physical activity, per hours per week	1.0 (−6.0 to 8.0)	.73	−2.0 (−9.0 to 4.0)	.49
Alcohol intake, per drinks per week	−0.1 (−1.0 to 1.0)	.70	−1.0 (−2.0 to 0.1)	.09
Smoking, per pack-year	3.0 (−0.2 to 6.0)	.06	4.0 (0.2 to 8.0)	.04
Peak $\dot{V}o_2$, per mL/kg/min	0.4 (−0.2 to 1.0)	.19		
Peak exercise diastolic blood pressure, per mm Hg	−1.0 (−1.4 to −0.4)	<.001		
Cholesterol/HDL ratio, per unit	−3.0 (−10.0 to 5.0)	.52		
HOMA- IR, per unit	−14.0 (−30 to 1.0)	.08		
Hypertension treatment (vs no treatment)	10 (−9.0 to 31.0)	.27		
Brain Vessel Tortuosity			R^2 = 0.1	.26
Gestational age, per week	0.005 (0.001 to 0.009)	.007	0.006 (0.001 to 0.01)	.01

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); HOMA-IR, homeostatic model assessment of insulin resistance; SBP, systolic blood pressure.

[a] Also modeled was the association between these risk factors and tortuosity, and only gestational age was related; full analysis is presented in the supplement (eTable 1). Model adjusted for nonmodifiable factors of age, sex, gestational age, and modifiable risk factors of systolic blood pressure, body mass index, vigorous physical activity, weekly alcohol consumption, and smoking status. Exposure variables were available for all participants. The point estimate refers to the magnitude of change in the vessel morphology variable per unit change in the nonmodifiable and modifiable variables.

P = .03). There was no significant correlation between blood arrival time and the cardiovascular scores (Table 3).

In multivariable analysis, controlling for modifiable risk factors (systolic blood pressure, BMI, vigorous physical activity, smoking, alcohol intake), blood arrival time and cerebral blood flow varied with cerebral vessel density, with each additional vessel per cm^3 correlating with a 0.015-second faster blood arrival time (95% CI, −0.03 to −0.002, *P* = .02) and 3-mL/100 g/min increase in cerebral blood flow (95% CI, 0.7 to 5.4, *P* = .01). Vessel density was inversely correlated with WMH lesion count, with 1.5 fewer lesions per unit increase in vessel density per cm^3 (95% CI, to −2.7 to −0.4, *P* = .01) (**Table 4**).

Discussion

In this cross-sectional study, optimal status of modifiable cardiovascular risk factors in young adults was associated with differences in brain vessel structure and function as well as a lower number of WMH lesions. Higher vessel density correlated with both higher cerebral blood flow and lower WMH lesion counts.

To date, studies tracking changes in brain vascular measures have largely focused on the transition from middle age to older adulthood. Cerebral blood flow is estimated to decline over the life course[26] with risk of dementia in older adults being 2- to 3-fold higher in those whose cerebral blood flow is below 55 mL/100 g/min.[27] Vascular dementia has also been associated with lower vascular density in brains of adults who have an early diagnosis of disease.[28] In the current study, young adults in the lowest tertile for the modifiable cardiovascular score had approximately 1-vessel/cm^3 lower vessel density and a mean value for cerebral blood flow of 55 mL/100 g/min, which is in the bottom 40% of the current study population. Therefore, the distribution of MRI findings observed in the current study raises the potential that some individuals may be starting to diverge to different risk trajectories for brain vascular health in early adulthood. Furthermore, levels of cerebral blood

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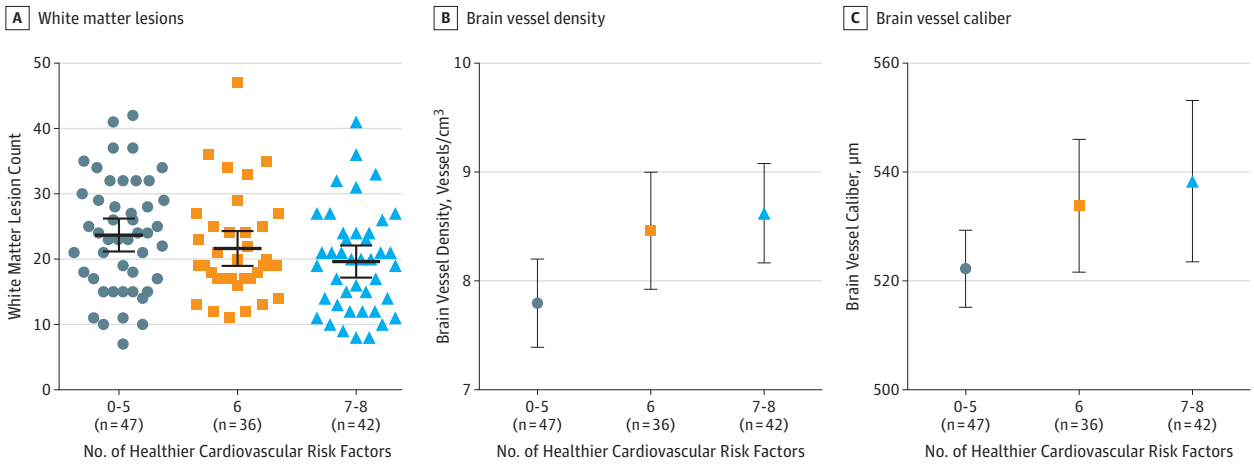
Table 3. Modifiable Cardiovascular Score and Association With Brain Vessel Morphology, Cerebral Blood Flow, and White Matter Hyperintensity Lesion Count[a]

Modifiable Cardiovascular Score	Point Estimate (95% CI)					
	Brain Vessel Density, Vessels/cm^3	Brain Vessel Caliber, μm	Brain Vessel Tortuosity	Brain Blood Arrival Time, s (n = 52)	Cerebral Blood Flow, mL/min/100 g (n = 52)	Brain White Matter Hyperintensity Lesion Count, No.
1 (n = 2) Worst	9.2 (6.4 to 11.9)	505 (437 to 573)	1.52 (1.44 to 1.50)			36.2 (24.3 to 48.0)
2 (n = 0)						
3 (n = 4)	6.9 (5.0 to 8.8)	518 (470 to 565)	1.49 (1.46 to 1.52)	1.26 (1.16 to 1.36)	66.6 (50.4 to 82.0)	24.0 (16 to 32)
4 (n = 14)	7.4 (6.6 to 8.2)	512 (493 to 532)	1.47 (1.45 to 1.53)	1.22 (1.16 to 1.27)	54.2 (45.5 to 63.0)	25.0 (21.0 to 29.2)
5 (n = 27)	8.0 (7.4 to 8.5)	524 (510 to 540)	1.51 (1.47 to 1.55)	1.21 (1.16 to 1.26)	54.6 (47.0 to 62.0)	22 (19.0 to 25.3)
6 (n = 36)	8.5 (8.0 to 9.0)	533 (521 to 545)	1.49 (1.46 to 1.52)	1.19 (1.15 to 1.23)	60.2 (54.0 to 67.0)	21.0 (19.0 to 24.0)
7 (n = 33)	8.5 (8.0 to 9.0)	542 (530 to 555)	1.48 (1.45 to 1.52)	1.18 (1.14 to 1.22)	64.0 (57.8 to 70.0)	19.0 (16.2 to 21.8)
8 (n = 9) Best	9.1 (8.2 to 10.0)	540 (518 to 563)	1.54 (1.46 to 1.62)	1.18 (1.11 to 1.24)	68.0 (57.6 to 78.1)	20.0 (15.4 to 26.6)
Change in point estimate per additional score unit (n = 125)	0.31 (0.112 to 0.514)	8.0 (3.0 to 13.0)	0.005 (−0.008 to 0.18)	−0.014 (−0.03 to 0.001)	2.5 (0.16 to 4.89)	−1.6 (−3.0 to −0.5)

[a] Participants were assessed for a cardiovascular score, for each healthier category of a modifiable risk factor according to the following criteria: BMI <25; highest tertile of cardiovascular fitness and/or physical activity; alcohol intake <8 drinks/week; nonsmoker for >6 mo; blood pressure on awake ambulatory monitoring <130/80 mm Hg; nonhypertensive diastolic response to exercise (peak diastolic blood pressure <90 mm Hg); total cholesterol <200 mg/dL; and fasting glucose <100 mg/dL. Adjusted for age and sex. The point estimate refers to the magnitude of change in the dependent variable per unit change in the modifiable cardiovascular score.

Figure. Comparison of White Matter Lesion Count and Vessel Morphology Based on Study Participants' Modifiable Cardiovascular Score



The cardiovascular score was cumulative based on each of the following factors: high cardiovascular fitness (top tertile of peak oxygen uptake [≥110% predicted peak oxygen uptake] or participating in ≥75 minutes of vigorous physical activity per week); not smoking in last 6 months; alcohol intake <8 drinks/week; ambulatory awake blood pressure <130/80 mm Hg; body mass index <25; fasting total cholesterol <200 mg/dL; fasting blood glucose <100 mg/dL; and diastolic blood pressure at peak exercise ≤90 mm Hg. The figure presents a post-hoc comparison between groups of participants who scored 0 to 5 positive factors (n = 47), 6 factors (n = 36), and 7 to 8 positive factors (n = 42). The groupings were defined to approximate tertiles of the combined cardiovascular score.

A, White matter lesion counts for individual participants. The group mean and 95% CI are shown with a point estimate and error bars.

B and C, Participants with 7 to 8 healthier categories of risk factor had a mean vessel density 11% higher than participants with 0 to 5 healthier categories of risk factor (panel B, 8.6 vessels/cm^3 [SD, 1.39] vs 7.8 vessels/cm^3 [SD, 1.21], P = .007), a mean vessel caliber 3% higher (panel C, 538 μm [SD, 21] vs 522 μm [SD, 45] P = .02), and on average 20% lower white matter hyperintensity lesion counts (panel A, 19.6 lesions [SD, 7.8] vs 23.5 lesions [SD, 8.6] P = .03). Group means and 95% CI are shown with a point estimate and error bars and reported group differences are adjusted for age and sex.

flow associated with an increased risk of dementia are evident in some young adults.

Adverse modifiable cardiovascular risk factors are major determinants of WMH progression,[29] with small lesions increasing in size or clustering into confluent lesions.[30] WMH lesion count was up to 4 lesions lower in the highest tertile of optimal status of modifiable risk factors. Accumulation of lesions from an early age might explain why, by mid-life, WMH lesion volume is an established predictor of future stroke and dementia risk.[5] The longitudinal relationships between vessel morphology, cerebral perfusion, and white matter lesion burden are uncertain. However, the patterns observed in the

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Table 4. Association of Vessel Morphology (Density, Caliber, Tortuosity) With Measures of Brain Blood Arrival Time, Cerebral Blood Flow, and White Matter Hyperintensity Lesions[a]

	Bivariable Point Estimate (95% CI)	*P* Value	Multivariable-Adjusted Point Estimate (95% CI)	*P* Value
Blood arrival time, s (n = 52)				
Brain vessel density, vessels/cm^3	−0.03 (−0.04 to −0.01)	.002	−0.015 (−0.03 to −0.002)	.02
Brain vessel caliber, μm	0.08 (−0.61 to 0.78)	.81	0.22 (−0.28 to 0.71)	.38
Brain vessel tortuosity	0.13 (−0.15 to 0.4)	0.36	−0.014 (−0.23 to 0.21)	.90
Cerebral blood flow, mL/100 g/min (n = 52)				
Brain vessel density, vessels/cm^3	4.0 (1.8 to 6.2)	.001	3.1 (0.7 to 5.4)	.01
Brain vessel caliber, μm	48.6 (−50.3 to 147.6)	.34	−8.0 (−126.1 to 110.1)	.89
Brain vessel tortuosity	3.8 (−36.4 to 44.1)	.85	12.9 (−35.4 to 61.1)	.60
White matter hyperintensity lesion count (n = 125)				
Brain vessel density, vessels/cm^3	−1.1 (−2.2 to 0.06)	.06	−1.5 (−2.7 to −0.4)	.01
Brain vessel caliber, μm	13.5 (−31.3 to 58.4)	.55	12.1 (−34.5 to 57.8)	.61
Brain vessel tortuosity	−17.5 (−35.3 to 0.24)	.053	−11.0 (−29.0 to 7.0)	.23

[a] Model adjusted for nonmodifiable factors of age, sex, and gestational age and modifiable risk factors of systolic blood pressure, body mass index, vigorous physical activity, weekly alcohol consumption, and smoking status. Also modeled was the association with vessel caliber and tortuosity; only vessel density was related. The point estimate refers to the magnitude of change in blood arrival time, cerebral blood flow, or number of white matter hyperintensity lesions per unit change in respective vessel morphological variable. Vessel tortuosity was defined by the deviation from the shortest path between 2 points. This analysis was implemented by identifying the vessel end points and bifurcations, calculating the shortest path and the length of the actual center line between each 2 connected points. The final tortuosity was then calculated by the ratio and it was averaged over all vessel segments.

current study may suggest that resilience of the white matter, and potential to withstand risk exposures, may be influenced by the vascular morphology of an individual.

Modifiable risk factors such as blood pressure, BMI, smoking, and lipid profile are known to drive systemic vascular disease in young adults in part through biological vascular disorders, including endothelial dysfunction and oxidative stress.[31-33] The current study suggests the cerebrovasculature may be similarly affected. Novel early life factors, such as preterm birth, are linked with early vascular disease[34] and the third trimester and early neonatal period are hypothesized to be times of significant vascular remodeling. In this study, gestational age was associated with vessel tortuosity, consistent with previous reports in infants,[35] but not other cerebrovascular measures. Further work is needed to understand whether this was because participants were largely born late preterm or because cardiovascular risk profile overwhelms this early exposure.[28]

The observed association between brain vascular measures and modifiable risk factors raises the potential for targeted intervention to prevent progression to disease. Reducing multiple risk factors can change risk trajectories and reduce vascular disease burden,[36] with sustained lifestyle intervention and active blood pressure lowering associated with lower burden of WMH lesions and improved cerebral perfusion.[37,38] These interventions typically achieve 25% improvements in cardiovascular fitness and 10-mm Hg reductions in blood pressure,[37,38] comparable to differences between high and low tertile groups for the cardiovascular scores in this study.

However, lifestyle-based primary cardiovascular prevention in young adults requires complex intervention design. A recent systematic review of interventions in young people with hypertension demonstrated that the optimal way to intervene is poorly understood with lack of sustained effect.[39] The alternative to lifestyle interventions would be pharmacological treatment. However, in this study group higher blood pressure was associated with reduced vessel density and antihypertensive use was associated with lower cerebral blood flow. Therefore, further work to identify optimal interventions in young adults to maintain autoregulation of cerebral blood flow, while reducing risk, may be required.

Limitations

This study has several limitations. First, a small sample recruited at a single site increases the risk of bias and type I error, while the study may be underpowered to identify subtle correlations with some risk factors. Second, purposive mixed passive and active recruitment strategies mean the sample is not population-based and could be considered similar to a convenience sample. Therefore, it is not possible to generalize expected prevalence of cerebrovascular changes to the wider population.

Third, the study is cross-sectional and causality or even temporality of the observed relationships cannot be inferred. Fourth, the cardiovascular risk assessment would be strengthened by detailed dietary questionnaires, which were not included in this study. Fifth, cerebral blood flow was only available in a subgroup, so the ability to understand interactive effects of modifiable risk factors, vascular remodeling, and perfusion on white matter integrity is limited. Sixth, longitudinal follow-up will be required to determine the clinical significance of the observed findings. As such, this study should be considered preliminary and exploratory but does support a need for future work. The complexity of the imaging protocol and associated financial costs may limit its widespread use, but large multicenter studies with more focused protocols, and extended follow-up, may have the potential to track vascular remodeling and evaluate the influence on white matter and the association with later disease.

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Conclusions

In this preliminary study involving young adults without clinical evidence of cerebrovascular disease, a greater number of modifiable cardiovascular risk factors at recommended levels was associated with higher cerebral vessel density and caliber, higher cerebral blood flow, and fewer white matter hyperintensities. Further research is needed to verify these findings and determine their clinical importance.

ARTICLE INFORMATION

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Supervision: Lewandowski, Forkert, McKean, Dawes, Foster, Leeson.
Other - Development of the brain MRI protocol and image analysis: Okell.

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